

39. (Amended) The method of any of claims 13-20 [38], wherein said PYY Therapeutic enhances or recovers glucose responsiveness.

45. (Amended) A method for maintaining or restoring normal pancreatic islet function, comprising administering to a cultured pancreatic islet or cell a PYY Therapeutic, thereby maintaining or restoring normal pancreatic islet function.

50. (Amended) The method of [any one of the above] claim[s] 21 [13-49], wherein said animal is a human.

### **REMARKS**

Claims 1-13 and 15-86 constitute the pending claims in the present application. Claims 1-12, 24-27, 34-38, 40, 41, 44, 47-49, and 52 are withdrawn as being directed to a non-elected invention. Applicants will cancel such claims upon indication of allowable subject matter. Applicants submit, however, that claims 25-27, 34-37, and 52, are properly dependent on elected independent claims and should be rejoined upon determining that such independent claims are allowable, pursuant to MPEP 809.02(c). Accordingly, these claims, too, are presented above. Applicants also submit that claims 42 and 43 are properly dependent on claim 41, not on claim 39 as filed, and thus are properly withdrawn with claim 41. Applicants regret any confusion this error may have caused. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants note that the change of address/power of attorney has been entered, and that the request for a corrected filing receipt has been entered.

Applicants note the election to prosecute the claims of group IV is final.

Applicants will submit formal drawings upon indication of allowable subject matter.

Applicants have amended the pending claims to remove improper multiply dependent claims. The dependency of claim 29 has also been corrected.

Claims 15 and 46 are objected to for allegedly failing to further limit the subject matter of a previous claim. Applicants direct the Examiner's attention to MPEP 608.01(n)(III), which points out that "[a] dependent claim does not lack compliance with 35 U.S.C. § 112, fourth paragraph, merely because there is a question as to (1) the significance of the further limitation added by the dependent claim, or (2) whether the further limitation in fact changes the scope of the dependent claim from that of the claim from which it depends." Additionally, with respect to claim 15, Applicants submit that the further limitation is not the result of a method step, but is a statement of a *property* of the islet or cell, and that one of skill in the art would readily comprehend the meaning of this claim. Applicants have amended claim 45 to overcome the Examiner's objection. Applicants submit that the scope of this claim is not narrowed by this amendment.

Applicants have corrected the specification at page 50 as suggested by the Examiner.

Claims 13-23, 28-32, 39, 42, 43, 50, and 51 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants have amended claim 13 to be directed to methods for altering the glucose-responsiveness of a pancreatic islet or cell, solely to expedite prosecution of the remaining claims. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

The Office Action alleges that the specification is enabled for PYY but not for the broader class of PYY therapeutics. Applicants submit, however, that as of the filing date, a number of other PYY analogs were available, as indicated by the references and abstracts provided herewith as Exhibit A. Additionally, column 3 of U.S. Patent 5,574,010, incorporated by reference in the specification at the bottom of page 23, points out a number of other references relating to compounds that fall within the scope of the term 'PYY Therapeutic'. The

art at the time of filing thus included a panoply of compounds that are ‘PYY Therapeutics’ as this term is used in the specification and pending claims. Furthermore, one of ordinary skill in the art using assays described in these references could have identified any number of additional PYY therapeutics using only routine experimentation. Applicants respectfully remind the Examiner that “[a] patent need not teach, and preferably omits, what is well known in the art.” MPEP 2164.01(a).

Applicants further direct the Examiner’s attention to MPEP 2164.04. This section delineates the Examiner’s burden “to establish a reasonable basis to question the enablement provided for the claimed invention.” Specifically, “it is incumbent upon the Patent Office, whenever a rejection on this basis, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.” *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). Additionally, the Federal Circuit recently articulated a standard whereby the PTO must establish a rational connection between the agency’s fact-findings and its ultimate action. *Dickinson v. Zurko*, 119 S.Ct. 1816 (1999). In light of the Applicants’ arguments of record, and the presumption in favor of Applicants, it is respectfully asserted that the present rejection is not supported by substantial evidence, and as such, fails to rise above the “arbitrary, capricious” standard applied under the “substantial evidence” test of Section 706(2)(E) of the Administrative Procedure Act. The Examiner has not cited any relevant art nor relied on any other fact-finding results to rebut the presumption in favor of Applicants. Accordingly, Applicants submit that the use of ‘PYY Therapeutics’ is fully enabled by the present specification and the level of skill in the art at the time of filing of the present application.

Lastly, the Office Action questions whether the *in vitro* results disclosed in the application would have been expected to function similarly *in vivo*. The Examiner has cited art suggesting that such correlation is unreliable. None of this art, however, relates to PYY Therapeutics in particular. Applicants submit herewith as Exhibit **B** a selection of abstracts that demonstrate that *in vivo* and *in vitro* functions of PYY show a strong correlation. For example, the abstract of Souli et al., *Peptides* **1997**, *18*, 551-557, teaches the correspondence of *in vivo* and *in vitro* results using PYY to inhibit VIP-induced fluid secretion in rat jejunum. Balasubramanian et al., *J. Med. Chem.* **2000**, *43*, 3420-3427, demonstrate that a variety of PYY

analogs that exhibit *in vitro* activity are also active *in vivo* in the intestine of dogs. Grise et al., *J. Surg. Res.* 1999, 82, 151-155, show that PYY inhibits growth of breast cancer *in vivo* and *in vitro* alike. Bertrand et al., *Pancreas* 1992, 7, 595-600, extend this correlation even to the insulin secretion functions of the pancreas. In light of these favorable results relating to the particular therapeutics contemplated by the present invention, Applicants submit that the generalized teachings cited by the Examiner fail to undermine the enablement of the presently claimed methods. Applicants submit that the knowledge in the art demonstrates a reasonable correlation between *in vivo* and *in vitro* results using PYY therapeutics that supports enablement of the pending claims. These results also counter the generalized concerns raised by the Examiner relating to biological stability, immunological activation, bioavailability, etc., as the successful use of PYY *in vivo* to affect various organs including the pancreas is clearly demonstrated by these abstracts.

In addition, Applicants submit herewith as Exhibit C selected pages from a continuation-in-part (U.S. Application No. 09/634,363, filed August 9, 2000) of the present application, which relates to successful use of PYY *in vivo* results to control glucose levels in rats predisposed to diabetes. These results indicate that the claimed methods, as disclosed in the present application, would have been effective as taught by Applicants at the time of filing. For all of the above reasons, which demonstrate that the present claims were enabled throughout their scope at the time of filing, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 13-23, 28-32, 39, 42, 43, 50, and 51 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

With respect to the term "PYY Therapeutic", the Office Action states that "[t]he metes and bounds of 'PYY Therapeutic' cannot be determined from the claims." Applicants respectfully point out, however, that the definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the application and the understanding of one of skill in the art. MPEP 2173.02. The specification defines the term 'PYY Therapeutic' at page 9, lines 24-25, and ensuing paragraphs provide additional examples that further elaborate the meaning of

this term. Applicants submit that the specification, such as at page 9, lines 30-34, clearly indicates that although a PYY Therapeutic may be employed *in* a composition, that it is the agent and not the composition that is the PYY Therapeutic.

With respect to the phrase “altering the differentiated state”, Applicant submits that it is not unclear whether this term refers to “causing the cell to differentiate, de-differentiate, or if it merely suggests any change in the cells.” Rather it is clear that the term encompasses all of these possibilities, and that the ordinary meaning of these words is sufficient to indicate to one of skill in the art that any alteration in the differentiated state is intended to be encompassed by this phrase. Reconsideration and withdrawal of this rejection is respectfully requested.

Applicants have replaced the term “modifying” in claim 21 with “altering”. Applicants submit that altering clarifies the subject matter being claimed, and this term is used consistently with its meaning as described in the previous paragraph as applied to claim 13. Applicants submit that the scope of the claim is not narrowed by this amendment.

Applicants have replaced the term “pharmaceutically effective amount” with “therapeutically effective amount”. Applicants direct the Examiner’s attention to *In re Caldwell*, 138 USPQ 243 (CCPA 1963). “[‘Effective amount’] may be from the least effective amount to the amount beyond which no further beneficial effect is observed.... ‘Effective amount’ admirably states what is to be derived from the disclosure of the specification as to amount.” Applicants point out that such terms have been repeatedly approved (see also *Rhone-Poulenc Agrochime S.A. v. Biagro Western Sales, Inc.*, 35 USPQ2d 1203, 1205 (E.D. Calif. 1995) (method for controlling fungus with an effective amount of compound is not indefinite)) and that the concerns raised over the use of “therapeutically effective amount” are legally unfounded. Applicants further submit that the scope of the claim is not narrowed by this amendment. Reconsideration and withdrawal of this rejection is respectfully requested.

The Office Action alleges that claim 33 is indefinite for failing to set forth any steps. Applicants have amended this claim to more clearly recite a step. Applicants are unaware of any legal requirement that two or more steps be included in the method as claimed. Applicants have amended the preamble to clarify the subject matter intended to be claimed Applicants submit that the scope of the claim is not narrowed by this amendment. Applicants further point out that claim

33 is not a 'use' claim as alleged by the Office Action, and that MPEP 2173.05(q) supports Applicants' position. The Examiner's attention is drawn particularly to the section entitled "Board held step of 'utilizing' was not indefinite". Applicants submit that the Office Action fails to establish grounds for rejection of claim 33 under 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of this rejection is respectfully requested.

The Office Action asserts that the phrase "pancreatic islet or cell" implies that the term "pancreatic islet" is used to refer also mean cell, a meaning repugnant to the art-recognized meaning of this term. Applicants submit, however, that the proposed interpretation would render the term "or cell" redundant, and that the term "pancreatic islet" is, in fact, used in the claims to refer to what is commonly understood in the art to be a pancreatic islet. Applicants are unclear as to why it is alleged that one of skill in the art would construe these terms any other way. Clarification is respectfully requested.

Claims 28-32, 39, 42, 43, and 50 have been corrected to depend only from elected claims. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 13, 21, 33, and 45 have been amended to more particularly point out that the recited step achieves the stated goal.

Claims 15, 30, 31, and 50 have been amended to provide antecedent basis for the recited terms. Claims 42 and 43, as has been pointed out above, should be withdrawn.

### **CONCLUSION**

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this Reply, please charge the fees to our **Deposit Account No. 18-1945**. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

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Respectfully Submitted,



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